REMARKS

Reconsideration of the rejections set forth in the Office action mailed May 4, 2006 is respectfully requested. Claims 1, 3-4, 6 and 15-21 are currently pending. Claim 7 is cancelled with this amendment and new claims 17-21 are added.

I. Amendments

Claim 1 is amended for clarity and in accordance with embodiments of the invention described in the specification. The amended claim reads as follows:

A method of synthesizing a repertoire of oligonucleotide tags, each having a predetermined length in the range of from 18 to 60 nucleotides, the method comprising the steps of:

(a) providing first and second libraries of same-length oligonucleotide tag precursors in first and second cloning vectors,

wherein each oligonucleotide tag precursor consists of two four-nucleotide words, and each word is selected from a minimally cross-hybridizing set of oligonucleotides, such that a duplex consisting of a word of the set and the complement of any other word of the set contains at least two mismatches;

(b) cleaving one such cloning vector, at two cleavage sites, to produce a first opened vector and a first excised fragment, said first excised fragment containing at most one word from said oligonucleotide tag precursor;

(c) separately cleaving the other such cloning vector, at two cleavage sites, to produce a second opened vector and a second excised fragment, said second excised fragment containing one or more words from said oligonucleotide tag precursor;

(d) ligating said second excised fragment, containing one or more words, into said first opened vector, thereby elongating said oligonucleotide tag precursors in said first vector;

(e) amplifying the elongated oligonucleotide tag precursors in said first vector; and

(f) repeating steps (b) through (e) until a repertoire of oligonucleotide tags having the predetermined length is formed.

Basis for Amendments

The use of "first and second libraries" using "first and second vectors" is described in working Example 3, where, in accordance with one embodiment, the first and second vectors (pUSCE and pLCV) are different (as in dependent claim 19). Figure 1a shows an embodiment of the invention employing a process similar to that used in Example 3, but where two aliquots of the same vector are used (i.e. in cleavage steps designated 114 and 116 in the Figure). This disclosure is pertinent to dependent claim 20.

Claim 1 is also amended, in accordance with working Example 3, to recite that the oligonucleotide tag precursors include two four-nucleotide words.

The language "amplicon, wherein said amplicon is a cloning vector" has been simplified to simply "cloning vector", and the term "amplicon" has accordingly been replaced with "vector" in the claims.

The description of minimally cross-hybridizing sets in which a duplex consisting of a word of the set and the complement of any other word of the set contains "at least two mismatches" (amended claim 1) finds support, for example, at page 4, lines 28-29. New dependent claims 18 and 21 recite minimally cross-hybridizing sets in which a duplex consisting of a word of the set and the complement of any other word of the set contains "at least three mismatches", as shown for a set of four-nucleotide words in Table 1 on page 8 of the specification.

Claim 1 has also been amended, for clarity, to state that the vectors are cleaved at two places (as is apparent, for example, from Figures 1-2), and the smaller fragments produced are termed "excised" fragments (see e.g. page 12, lines 13-14).

Dependent claims which are made redundant by the amendments to claim 1 have been amended or cancelled (claim 7) accordingly.

No new matter is added by any of the amendments.

II. Rejections under 35 U.S.C. §112, First Paragraph

The pending claims were again rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention without undue experimentation.

This rejection is respectfully traversed for the following reasons.

Firstly, the Examiner's observations in items 4, 5, 6, and 8 of the Office Action (pages 3-5) are based on a misreading and misinterpretation of the claim language. The Examiner reads the claims as stating that: "a word of the [minimally cross-hybridizing] set and the complement of any word of the set contains a number of mismatches that is either 1, 2, or 3 less than the length, in terms of nucleotides, of the word" (Office Action, top of page 4). The Examiner therefore concludes that the words are not complementary to their antiparallel strands (item 5), and that the duplex structures contain "a large percentage of mismatches" (items 6 and 8).

The claims actually state that "a word of the [minimally cross-hybridizing] set and the complement of any **other** word of the set contains [a specified minimal number of mismatches]" (emphasis added). That is, a "word" in the set rarely cross-hybridizes with the complements of other "words" in the set (hence the term "minimally cross-hybridizing set"). This produces high accuracy in sorting using tags constructed from these "words", as noted in the specification at, for example, page 2, lines 29-30.

Therefore, the Examiner's conclusion that the vectors or other duplex structures used in the method have "a large percentage of mismatches" is inaccurate.

With respect to item 7 of the Office Action (page 4), the independent claim has been amended to explicitly state that the vector is cleaved in two places, such that an excised fragment is produced.

At item 10 and following, the Examiner reiterates his previous allegation that the specification does not teach the skilled artisan how to use the claimed invention, how to synthesize "only useful oligonucleotide tags", or how to "recognize useful over non-useful oligonucleotides or vectors". This conclusion is traversed for the following reasons.

As described in the specification (e.g. page 2, lines 16-30; page 4, lines 23-35; and page 8, lines 5-6 and Table 1), and recited in the claims, the oligonucleotide tags prepared by the method of the invention are not random sequence oligonucleotides, as the Examiner seems to imply. Rather, they are made up of "a plurality of words, or oligonucleotide subunits, that are

selected from the same minimally cross-hybridizing set of oligonucleotides, such that a duplex or triplex consisting of a word of the set and the complement of any other word of the same set contains at least two mismatches", and preferably a larger number of mismatches (page 4, lines 23-35).

The usefulness of tags constructed from these sets of "words" is described, for example, in the Background of the specification: "Such repertoires [of tags] permit tagging and sorting of molecules with a much higher degree of specificity than ordinary oligonucleotides" (page 2, lines 29-30).

Examples of such minimally cross-hybridizing sets of words are provided in Table 1 on page 8, as well as in the patent publications incorporated by reference on page 4 of the specification. Thus, a skilled person could clearly select sets of "words" to construct useful tags for sorting, using the method of the invention.

The applicant also disagrees with the Examiner's statement that the current situation is "analogous" to that considered in *Genentech v. Novo Nordisk A/S*, 42 USPQ2d 1001. Genentech sought to claim a process for obtaining hGH unaccompanied by a leader sequence or other extraneous proteins, by cleaving an hGH-containing conjugate protein. A review of that case shows that the Court observed that "no one had been able to produce any human protein via cleavable fusion expression as of the application date" of Genentech's application.

The Court in *Genentech* pointed out that the specification must supply the "novel aspects" of an invention. Since Genentech was attempting to claim a specific application of a process which, at the time of filing, no one had been able to successfully carry out for any starting material, starting materials and reaction conditions would indeed be novel aspects of their invention.

In the present case, on the contrary, the sets of "words" used in the applicant's claimed process, and their usefulness in constructing oligonucleotide tags, are described in the specification and had been fully described in the applicant's earlier work, which is cited and incorporated by reference in the specification (e.g. in the definition of "word" on page 4 of the specification). The processes used in the individual steps of the claimed method (e.g.,

cleaving with endonucleases, ligating, amplifying) are standard processes in genetic engineering.

More pertinent case law for the present situation includes *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 USPQ2d 1225 (Fed. Cir. 1999):

> Section 112, paragraph 1 "permits resort to material outside of the specification in order to satisfy the enablement portion of the statute because it makes no sense to encumber the specification of a patent with all the knowledge of the past concerning how to make and use the claimed invention."

and *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.*, 166 F.3d 1190, 49 USPQ2d 1671 (Fed. Cir. 1999):

> "The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation."

In view of the foregoing, the applicants submit that the claims are in accordance with the requirements of 35 U.S.C. §112, first paragraph.

III. Rejections under 35 U.S.C. §101

The pending claims were again rejected under 35 U.S.C. §101 as lacking a specific and substantial asserted utility or a well-established utility.

The Examiner alludes to cases dealing with claims to ESTs, as if the words and tags described in the specification were random sequence oligonucleotides. This is clearly not the case, as pointed out above.

Further in this vein, the Examiner asserts that the tags prepared by the presently claimed process could only be used "to determine if a complementary sequence is present" and thus have no specific utility. This assertion is contradicted by the specification. As stated in the Field of the Invention, the collections, or repertoires, of oligonucleotide tags provided by the invention can be used "for identifying, sorting, and/or tracking molecules, especially polynucleotides" (page 1, lines 8-9 of specification). The superiority of tags constructed from these sets of "words" to "ordinary oligonucleotide" is noted, for example, in the Background

of the specification: "Such repertoires [of tags] permit tagging and sorting of molecules with a much higher degree of specificity than ordinary oligonucleotides" (page 2, lines 29-30).

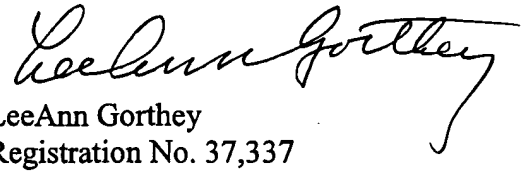
The use of such oligonucleotide tags is described further in the definition of a "word" at page 4, line 30, where the Brenner reference noted above, as well as further US patent documents, are incorporated by reference. The "words" are clearly not random sequences of nucleotides, as implied by the Examiner. The incorporated references provide algorithms for generating minimally cross-hybridizing sets of words, as noted at page 8, lines 4-6. Exemplary minimally cross-hybridizing sets of words are also provided at pages 7-8 of the current specification. The skilled person would thus know how to select "useful" oligonucleotides (words and tag precursors) for carrying out the invention, and would know how to use the end product (tags).

In view of the above, the applicants submit that the claims are in accordance with the requirements of 35 U.S.C. §101.

IV. Conclusion

In view of the foregoing, the applicants submit that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

Respectfully submitted,



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